REMARKS

The Office Action has been carefully reviewed. No claim is allowed. Claims 5, 9, 11, 12 and 15-18 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claim 9 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the amendment to claim 9.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 5, 9 and 11-18 have been rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description for leptin homologues and derivatives. This rejection is respectfully traversed.

Claim 9 is amended to recite that the fragment, homologue or chemical derivative of leptin all have the activity of leptin and that the leptin homologue has at least 90% sequence identity to the sequence of leptin, a known and well-defined protein, whereas the chemical derivatives of leptin are now recited as having one or more chemical moieties attached to leptin. Certainly for the chemical derivatives of leptin, the conserved structure is leptin itself, with the one or more chemical moieties, i.e., polyethylene glycol, only being attached

to the leptin core. A copy of WO 00/47741 is attached hereto to show an example of other chemical moieties added to leptin by glycosylation (see particularly pages 19-25).

With regard to leptin homologues, the homologues are limited to those that have at least 90% sequence identity to the leptin sequence. Attached hereto are copies of WO 96/05309 (equivalent to GB2292382 cited in the present specification) and U.S. Patent 5,831,017, which disclose muteins/variants/analogs/ homologues of leptin at columns 2-3 and 5-15 of US'017 and at pages 5 and 6 and page 37, line 25 to page 40, line 10 of WO'309. As numerous representative examples of leptin homologues are known in the art and there is guidance as to what residues are amendable to substitution, it is submitted that such representative examples of leptin homologues in the art serve as written description, which need not be specifically repeated in the present specification.

Moreover, applicants wish to point out that the instant claims at issue are method of use claims and not product claims. Applicants are not claiming novel products that have anti-angiogenic activity but rather the use of such products (leptin, fragments, homologues, or chemical derivatives thereof). Thus, the level of written description (and enablement) for a method of using a product, either in the specification or present in the prior art, should be much less than the standard required for a

product *per se* in order to satisfy the requirements of §112, first paragraph. Accordingly, the specification provides adequate written description for the present claims.

Insofar as the fragments of leptin, as presently recited in amended claim 9, are concerned, such fragments are supported by the present specification at page 17, lines 19-21. The attached WO'309 reference also provides adequate description of representative fragments of leptin which has leptin activity, thereby satisfying the written description requirements.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 5, 9 and 11-18 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. This rejection is respectfully traversed.

The examiner states that applicants' arguments have been fully considered but they are not persuasive because the specification discloses that the administration of leptin inhibits angiogenesis in ob -/- mouse but not in normal mouse. This characterization is not quite correct. In Example 1 on page 24 of the instant specification, ob -/- mice were used as a model system to test the anti-angiogenic effect of leptin; however, it is not that no anti-angiogenic effect was observed for leptin in normal mice but simply that no experiments were conducted in normal mice.

The Cohen et al. reference (*J. Biol. Chem.* 276, 2001), attached to the amendment of July 12, 2006, and made of record, teaches in the abstract:

> This tissue-specific induction of Ang-2 coincided with initiation of apoptosis in adipose endothelial cells. We propose that induction of Ang-2 by leptin in adipose cells is one of the events leading to adipose tissue regression.

Cohen further teaches in the left column of page 7699 that leptin induced Ang-2 mRNA expression in differentiated 3T3-F442A murine adipocytes (not from ob -/- mice) in an autocrine manner and also teaches in the bottom of the right column that leptin appears to be a very potent inducer of Ang-2 as compared with the previously reported agents VEGF, bFGF, hypoxia, and TNFα. As the same effect of leptin was observed in tissues and cells from ob -/- and normal mice, one of skill in the art would expect that the anti-angiogenic activity of leptin discovered in the ob -/- mouse model would also be found in normal mice as well. There is no reason to doubt this.

The examiner has also taken the position that, even if the administration of leptin inhibits angiogenesis, the specification does not enable one of skill in the art for inhibiting angiogenesis by administering leptin homologues having 80% or 90% sequence homology with the leptin sequence.

In view of the very substantial degree of identity that is necessary for leptin homologues in the present claims, it

would not take undue experimentation to test any such homologues using the 48 hr. assay in ob -/- mice taught in Example 1 of the instant specification. It is not necessary to know, or to be able to predict in advance, which variations in the amino acid sequence of leptin would maintain the ability of leptin to inhibit angiogenesis. It is not necessary to decide whether protein chemistry is predictable or unpredictable. The point is that mutations in the DNA-encoding leptin can be randomly made in a manner so as not to result in more than 10% variation in the encoded protein. Any such variants that have anti-angiogenic activity would fall within the scope of the claim. Anything else does not. These steps do not involve undue experimentation.

The amount of experimentation that may be permitted in order to satisfy the enablement requirement of 35 U.S.C. §112 is discussed in *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In this regard, *Wands* states, 858 F.2d at 736-737, 8 USPQ2d at 1404:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. "The key word is 'undue,' not 'experimentation.'"
>
> > The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d

> 872, 878-879; 169 USPQ 759, 762-763 (2d Cir. 1971), *cert. denied,* 404 U.S. 1018, 30 L. Ed. 2d 666, 92 S. Ct 680 (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed***. [Footnotes omitted - the latter quote being from *In re Jackson,* 217 USPQ 804, 807 (Bd. App. 1982)]

Wands goes on to state, 858 F.2d at 737, 8 USPQ2d at 1404:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. [Footnotes omitted]

In analyzing these factors in this case, the conclusion must be reached that the experimentation is not undue. As to the first factor, the quantity of experimentation may be significant, as mutations would have to be generated and screening conducted. However, in the *Wands* case, it was found that routine screening does not necessarily amount to undue experimentation.

With respect to the second factor, the amount of guidance or direction presented, the specification states, at page 11, lines 13-15:

> These homologues are prepared by known synthesis and/or by site-directed mutagenesis techniques, or any other known techniques suitable therefor.

Less guidance is needed for such well-known techniques. Substantial guidance as to a specific screen is provided in Example 1 at pages 24-25 of the present specification.

As to the third factor, the presence or absence of working examples, the assays in Examples 1-4 are sufficiently detailed to serve as working examples.

As to the fourth factor, the nature of the invention, the nature of the invention is such that substantial experimentation is acceptable. As will be discussed in the following factors, the field of this invention requires a very high level of skill in the art, and practitioners are well inured to screening that takes substantial experimentation quantitatively.

As to the fifth factor, the state of the prior art, synthesis and site-directed mutagenesis techniques are all well-documented in the prior art. The present invention does not involve any of these specific techniques *per se*. Their use on the sequence used in the method of the present invention would be well within the skill of those in the art.

As to the sixth factor, the relative skill of those in the art, those of ordinary skill in the art of recombinant DNA technology is very high, usually requiring a Ph.D. and/or substantial laboratory experience. For such persons, a greater amount of experimentation would be considered to be routine than for technologies requiring a lower level of skill in the art.

As to the seventh factor, the predictability of the art, predictability is not relevant here, as no predictability is necessary. One need only do the experiments and screen; the results will provide all of the answers. It is not necessary to predict the answers in advance.

As to the eighth factor, the breadth of the claims, claim 9 is not so broad so as to require undue experimentation to find what would fall within it for the reasons as discussed above with respect to all of the other factors.

Accordingly, as in *In re Wands*, analysis of the facts of the present case, considering the factors enumerated in *Ex parte Forman*, leads to the conclusion that undue experimentation would not be required to practice the invention. There was a high level of skill in the art at the time when the application was filed and all of the methods needed to practice the invention were well known. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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